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Copeptin adds prognostic information after ischemic stroke: results from the CoRisk study

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Abstract: **OBJECTIVE:** To evaluate and validate the incremental value of copeptin in the prediction of outcome and complications as compared with established clinical variables. **METHODS:** In this prospective, multicenter, cohort study, we measured copeptin in the emergency room within 24 hours from symptom onset in 783 patients with acute ischemic stroke. The 2 primary end points were unfavorable functional outcome (modified Rankin Scale score 3-6) and mortality within 90 days. Secondary end points were any of 5 prespecified complications during hospitalization. **RESULTS:** In multivariate analysis, higher copeptin independently predicted unfavorable outcome (adjusted odds ratio 2.17 for any 10-fold copeptin increase [95% confidence interval CI, 1.46-3.22], $p < 0.001$), mortality (adjusted hazard ratio 2.40 for any 10-fold copeptin increase [95% CI, 1.60-3.60], $p < 0.001$), and complications (adjusted odds ratio 1.93 for any 10-fold copeptin increase [95% CI, 1.33-2.80], $p = 0.001$). The discriminatory accuracy, calculated with the area under the receiver operating characteristic curve, improved significantly for all end points when adding copeptin to the NIH Stroke Scale score and the multivariate models. Moreover, the combination of copeptin with a validated score encompassing both the NIH Stroke Scale and age led to a net reclassification improvement of 11.8% for functional outcome and of 37.2% for mortality. **CONCLUSIONS:** In patients with ischemic stroke, copeptin is a validated blood marker that adds predictive information for functional outcome and mortality at 3 months beyond stroke severity and age. Copeptin seems to be a promising new blood marker for prediction of in-hospital complications.

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Copeptin Adds Prognostic Information After Ischemic Stroke:

Results From the CoRisk Study.

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Authors Contribution:

As principal investigators, Dr De Marchis (GMDM), Dr Katan (MK) and Dr Arnold (MA) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Katan, De Marchis, Christ-Crain, Mueller

Acquisition of data: De Marchis, Weck, Fluri, Gensicke, Foerch, Findling

Analysis and interpretation of data: De Marchis, Katan, Schütz, Arnold

Drafting of the manuscript: De Marchis and Katan

Critical revision of the manuscript for important intellectual content: Katan, De Marchis, Arnold, Christ-Crain, Mattle, Müller, Schuetz, Fluri, Foerch, Morgenthaler, Seiler, Weck, Findling, Gensicke, Buhl

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Study supervision: Katan and Arnold

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Clinical Trial Registration Information: This study is registered in ClinicalTrials.gov, unique identifier NCT00878813, <http://www.clinicaltrials.gov/ct2/show/NCT00878813>.

Key words: biomarker ■ copeptin ■ stroke ■ prognosis ■ mortality ■ complications

Abstract

Objective: To evaluate and validate the incremental value of copeptin in the prediction of outcome and complications as compared to established clinical variables.

Methods: In this prospective, multicenter cohort study we measured copeptin in the emergency room within 24 hours from symptom onset in 783 patients with acute ischemic stroke. The two primary endpoints were unfavorable functional outcome (modified Rankin Scale score 3-6) and mortality within 90 days. Secondary endpoints were any of five pre-specified complications during hospitalization.

Results: In multivariate analysis, higher copeptin independently predicted unfavorable outcome (adjusted OR 2.17 for any 10-fold copeptin increase [95% CI, 1.46–3.22], $P<0.001$), mortality (adjusted HR 2.40 for any 10-fold copeptin increase [95% CI, 1.60–3.60], $P<0.001$) and complications (adjusted OR for any 10-fold copeptin increase 1.93 [95% CI, 1.33–2.80], $P=0.001$). The discriminatory accuracy, calculated with the area under the receiver operating characteristics curve, improved significantly for all endpoints when adding copeptin to the National Institute of Health Stroke Scale (NIHSS) score and the multivariate models. Moreover, the combination of copeptin with a validated score encompassing both the NIHSS and age led to a net reclassification improvement (NRI) of 11.8% for functional outcome and of 37.2% for mortality.

Conclusions: In patients with ischemic stroke, copeptin is a validated blood marker that adds predictive information for functional outcome and mortality at three months beyond stroke severity and age. Copeptin appears as a new promising blood marker for prediction of in-hospital complications.

Introduction

Accurate and prompt prediction of functional outcome, mortality, and complications in patients with ischemic stroke are essential for patients, families, and clinicians. In this context, rapidly measurable and reliable blood biomarkers may refine clinical decision-making. Several blood biomarkers have shown the potential to predict outcome after ischemic stroke. However, in order to be useful in clinical routine, blood biomarkers are expected to improve the prognostic accuracy of established clinical variables such as stroke severity and age.¹ At present, either the investigated biomarkers have failed to further improve prognostication after stroke, or they have not been studied concerning their additional prognostic value.^{1,2} However, a recent single-center study showed that copeptin, a hypothalamic hormone derived from the precursor of vasopressin, predicted outcome and mortality three months and one year after ischemic stroke, improving the prognostic accuracy of established predictors.^{3,4} Copeptin is a reliable prognostic marker not only in stroke patients but also in patients with cardiovascular events.^{5,6} However, before implementing copeptin in clinical practice, the prognostic potential of copeptin needs to be validated in a prospective, independent, large multicenter study. Moreover, it is unclear whether copeptin predicts outcome in patients with ischemic stroke that has been treated differently, i.e. conservatively or with thrombolysis. The CoRisk study aimed to validate in a multicenter, international setting the accuracy of copeptin in predicting functional outcome, mortality, and complications as compared to established clinical variables.

Methods

Ethics Statement

This study (*ClinicalTrials.gov*: NCT00878813) was conducted according to the principles expressed in the Declaration of Helsinki and it was approved by the Ethics Committees. All patients or their welfare guardians provided written informed consent for the collection of data, blood samples, and subsequent analyses.

Study design and cohort description

The primary design of this multicenter prospective cohort study has been described in detail previously.⁷ For the analysis of this study we included 788 patients older than 18 years with an acute ischemic stroke within 24 hours of symptom onset, admitted consecutively to the emergency department of each tertiary care center between March 24, 2009 and April 8, 2011.

We defined acute ischemic stroke according to the World-Health-Organization Criteria as an acute focal neurological deficit lasting longer than 24 hours⁸ with no sign of acute intracranial bleeding on cerebral imaging. Exclusion criteria were missing informed consent or any diagnosis different from ischemic stroke (i.e. stroke mimics). Stroke physicians prospectively recorded the National Institute of Health Stroke Scale score (NIHSS)⁹ upon admission. The clinical stroke syndrome was assessed according to the Oxfordshire Community Stroke Project classification.¹⁰ Computed Tomography (CT) or Magnetic Resonance (MR) imaging was performed upon admission. MR imaging with diffusion-weighted imaging (DWI) was performed in 537 stroke patients. DWI lesion volumes were measured by the consensus of two experienced raters unaware of the clinical and laboratory findings. The lesion size was calculated by a commonly used semi-quantitative method validated for ischemic stroke lesions.¹¹ Lesions were categorized into three size classes to

represent typical stroke patterns: i) small lesion with a volume of $< 10 \text{ mm}^3$, ii) medium lesion of $10\text{--}100 \text{ mm}^3$, iii) large lesion with a volume of more than 100 mm^3 .³

Detailed information such as cardiac and neurovascular ultrasound and 24-hour ECGs were collected to define stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.¹² Comorbidities were assessed on admission by the modified Charlson-Comorbidity-Index.¹³

Biomarker Measurement

Blood was drawn in the emergency room, and within 24 hours of symptom onset, for all patients. After centrifugation for 20 minutes at $3'000g$ at room temperature, plasma (from EDTA tube) was aliquoted. Tubes were frozen locally at each center at -70°C . Copeptin levels were assessed in plasma in a blinded batch-analysis by a new chemiluminescence-sandwich-immunoassay. The lower detection limit was 0.4 pmol/l and the functional assay sensitivity was $< 1 \text{ pmol/l}$ ($< 20\%$ inter-assay coefficient of variation, defined as the ratio of the standard deviation to the mean). In 359 healthy individuals, median copeptin levels were reported to be 4.2 pmol/l with a 99th percentile of 13.5 pmol/l .¹⁴

Ascertainment of Outcomes

Trained stroke physicians and study nurses assessed outcome three months after the acute stroke, either during an outpatient visit (patients who underwent thrombolysis) or with a structured follow-up telephone interview. They were blinded to copeptin levels and baseline clinical variables.

Primary Endpoints: The two primary endpoints were (1) unfavorable functional outcome (including mortality) defined as a modified Rankin Scale (mRS) score of 3 to 6, and (2) mortality within 90 days of hospital admission.

Secondary Endpoint: The secondary outcome included any of the following pre-specified⁷

complications during hospital stay: symptomatic intracerebral hemorrhage (sICH) according to the SITS-MOST criteria¹⁵, space-occupying cerebral edema, pneumonia (defined as auscultatory respiratory crackles combined with body temperature ≥ 38 °C, purulent sputum, or positive chest x-ray), seizures (clinical diagnosis of focal and/or generalized seizure in a previously non-epileptic patient), or mortality within 10 days from stroke onset.

Statistical Analysis

Univariate Analysis: Statistical analysis was performed for the primary and the secondary endpoints separately. Discrete variables were expressed as counts (percentages) and continuous variables as means \pm standard deviations (SD) or medians (interquartile range), depending on their distribution. The distribution of raw biomarker data was skewed. After log transformation with a base of 10, the distribution of the biomarker data approximated a normal distribution. Comparisons for categorical baseline measurements were performed by Fisher's exact test and for continuous, not normally distributed baseline data, by the Mann-Whitney-U test. For survival analysis, we stratified patients according to copeptin tertiles in Kaplan Meier curves and compared the groups by mean of the logrank test.

Multivariate Regression Models: To assess the independent association of copeptin with functional outcome and time to fatal outcome within 3 months, we computed a multivariate logistic and cox regression model, respectively. We pre-specified that models were adjusted for NIHSS, age, and lesion size, modified Charlson Index¹³ and Total Anterior Circulation Stroke (TACS)¹⁰ based on the results of the previous derivation study.³ In addition, the final multivariate models included variables significantly associated with an unfavorable outcome or mortality in the univariate analyses. As patients with severe stroke tend to present earlier, time from symptom onset to blood collection was included in the final model.¹⁶ We report odds and hazard ratios (OR and HR) along with 95% confidence intervals as measure of association and uncertainty, respectively. OR and HR correspond to a one-unit increase in the

explanatory variable and to any 10-fold increase in copeptin, glucose or CRP levels (log-transformed with a base of 10). Goodness-of-fit of the multivariate logistic and cox regression models were assessed with the Hosmer-Lemeshow test and with Groennesby and Borgan test, respectively.

Interaction Analysis: We further included interaction terms to investigate if the predictive value of copeptin is modified by treatment status (conservative vs. thrombolysis), gender, age, stroke-severity (NIHSS 0–6; NIHSS 7–15; NIHSS > 15), time from symptom onset, blood collection (dichotomized at 4.5 hours), arterial hypertension, diabetes mellitus and atrial fibrillation. Selection of variables that were tested for interaction was based on biological plausibility on factors that might influence the prognostic value copeptin. NIHSS was categorized in order to represent clinically relevant stroke severity subgroups (mild, moderate and severe strokes), and time from symptom onset was dichotomized to represent the time window for intravenous thrombolysis.

C-statistics: The discriminatory value of copeptin was assessed with the area under the receiver-operating-characteristic curve (AUC). The incremental discriminatory value of copeptin was tested by comparing the AUC of the NIHSS (nested model), our prespecified prognostic factor of reference⁷, with the AUC of the NIHSS and copeptin (whole model), as well as comparing the logistic and cox regression models *without* copeptin (nested models) to the same models *with* copeptin (whole models). For these comparisons of nested to whole models, we used the likelihood ratio test as recommended.¹⁷

Reclassification Tables:

For risk model of comparison, we employed the multivariate models described above. As recommended in the statistical literature¹⁸, we calculated continuous (category-free) NRIs since our multivariate models of comparisons have no validated risk categories. To calculate category-based NRIs, we employed the validated prognostic index by König IR *et al*,

encompassing admission NIHSS and age.¹⁹ Four risk categories were chosen: 0-5%, 5-10%, 10-15%, >15%.

Statistics were calculated using *Stata Statistical Software: Release 12* (StataCorp LP, College Station, TX, 2011). For reclassification tables, we employed R version R 2.15.1 along with the PredictABEL package (version 1.2-1) available from CRAN repository (<http://cran.r-project.org/>). Testing was two-sided and *P* values less than 0.05 were considered to indicate statistical significance.

Results

Study Population

From March 24, 2009 through April 8, 2011 we consecutively recruited 788 patients with ischemic stroke. Stroke treatment was conservative in 465 patients (59.4%), and 318 patients (40.6%) underwent thrombolysis. Follow-up was available in 783 patients (follow-up rate: 99.6%). The detailed patient flow is outlined in Figure 1.

The median age of the cohort was 71.0 years (IQR 60.5–80.0), and 38.1% of the patients were women. The most common cardiovascular risk factor was arterial hypertension, which was present in 68.8% of patients. At admission, the median NIHSS score was 6 (IQR 3–13), and the median copeptin concentration was 14.2 pmol/l (IQR 5.9–46.5)(Table 1).

Primary Endpoints

(1) Prediction of Functional Outcome after Three Months

A total of 300 (38.3%) patients had an unfavorable outcome after three months. Median copeptin concentration was more than three-fold higher in patients with unfavorable outcomes than in those with favorable outcomes (Table 1, Figure e-1). In the multivariate logistic regression model, higher copeptin concentrations independently predicted an

unfavorable outcome (adjusted OR for any 10-fold copeptin increase 2.17 [95% CI, 1.46–3.22]). For instance, for a patient with a copeptin level of 30.0 pmol/l, the odds of unfavorable outcome are on average 2.17 times or 117% higher compared to a patient with a copeptin level of 3.0 pmol/l, after adjustment for the covariates included in the logistic regression model presented in table 2. The multivariate logistic model was well calibrated as assessed by the Hosmer and Lemeshow goodness-of-fit test ($P=0.62$).

The discriminatory accuracy of copeptin, assessed with the area under the ROC curve, was 0.71 (95% CI, 0.67–0.75). Copeptin significantly improved the discriminatory accuracy of the NIHSS and the multivariate logistic regression model both for an unfavorable functional outcome, defined as mRS 3-6, (Table 3, Figures e-2 through e-4) and disability, defined as mRS 3-5, (Table e-3).

Copeptin improved classification of patients when added to the validated prognostic index of Koenig *et al* ¹⁹ with a categorical NRI of 11.8% (Table e-4). Among patients with a favorable outcome, a total of 11.8% were moved to lower risk categories, while a net of zero patients with an unfavorable outcome was correctly reclassified. Moreover, adding copeptin to the full model improved reclassification as evidenced by the continuous NRI of 46.8%.

(2) Prediction of Mortality within Three Months after Stroke

A total of 118 (15.1%) patients died within three months after stroke. The median copeptin concentration was more than five-fold higher in patients who died within three months as compared to survivors (58.8 pmol/l [IQR 23.0–141.0] vs. 11.7 pmol/l [IQR 5.6–35.1], $P<0.001$) (Table e-1, Figure e-1). Overall, Kaplan–Meier survival curves of patients stratified per copeptin tertiles differed ($P<0.001$, logrank test) (Figure 2). In the multivariate cox model, higher copeptin concentrations independently predicted mortality (adjusted HR for any 10-fold copeptin increase 2.40 [95% CI, 1.60–3.60], $P<0.001$) (Table 2). The multivariate cox model was well calibrated as assessed by the Groennesby and Borgan test

($P=0.35$). The overall discriminative ability of copeptin to distinguish survivors from non-survivors – assessed with the area under the ROC curve – was 0.75 (95% CI, 0.71–0.80) (Figures e-5 through e-7). Copeptin significantly improved the discriminatory accuracy of the NIHSS and the multivariate cox regression model (Table 3). These results were also confirmed in reclassification statistics where the categorical NRI of copeptin upon the validated prognostic index of Koenig *et al* was 37.2% (Table e-5). Among survivors, a net of 33.0% were moved to lower risk categories, while a net of 4.2% of patients dead at three months were moved to higher risk categories. Moreover, adding copeptin to the multivariate model resulted in a continuous NRI of 64.5%.

Interaction Analysis

The predictive value of copeptin regarding functional outcome and mortality was consistent across all subgroups. We did not identify any significant effect modifiers.

Secondary Endpoint: Prediction of Complications

A total of 185 patients (23.6%) suffered from at least one of the five predefined complications during hospitalization. Median copeptin levels were more than three-fold higher in patients developing any of the pre-specified complications during hospitalization (39.9 pmol/l [IQR, 16.4–114.0] vs. 11.0 pmol/l [IQR, 5.3–32.5], $P<0.001$) (Table e-2). In the multivariate logistic model, copeptin independently predicted the occurrence of at least one complication (adjusted OR for any 10-fold copeptin increase 1.93 [95% CI, 1.33–2.80], $P=0.001$). Other significant predictors were the NIHSS and age. Copeptin improved the prognostic accuracy of the NIHSS (AUC change from 0.79 [95% CI, 0.76–0.83] to 0.80 [95% CI, 0.77–0.84], $P=0.001$). We found no significant interaction between copeptin and each of the potentially effect-modifying variables used for the primary outcomes. Prediction of individual complications was associated with different OR for any 10-fold copeptin

increase: for sICH, OR 1.07 (95% CI, 0.45-2.53, $P=0.89$); for space-occupying cerebral edema, OR 2.85 (95% CI, 1.39-5.87, $P=0.004$); for pneumonia, OR 1.79 (95% CI, 1.16-2.76, $P=0.009$); for seizures, OR 1.20 (95% CI, 0.62-2.33, $P=0.59$); for mortality within 10 days from admission, OR 3.00 (95% CI, 1.67-5.39, $P<0.001$).

Discussion

In this prospective multicenter study, higher copeptin blood levels independently predicted functional outcome and mortality three months after ischemic stroke. Copeptin improved the discriminatory ability of the NIHSS and multivariate models as shown by an increase in the respective AUCs. Despite the modest size of the AUC increases, copeptin improved risk classification by 11.8% for functional outcome and by 37.2% for mortality compared to the validated prognostic index by König *et al*, encompassing NIHSS and age.¹⁹ Moreover, copeptin improved reclassification compared to the multivariate models including demographic factors, cardiovascular risk factors, lesion size in MR, comorbidities, and admission laboratory variables such as CRP and glucose. The CoRisk study confirms and extends the conclusions of the previously published derivation study³. Further new findings are that (1) copeptin independently predicts complications, and (2) the prognostic ability of copeptin was consistent across subgroups including different acute treatments (conservative vs. thrombolysis).

While several markers, such as NT-BNP,^{5, 20, 21} CRP,²¹⁻²⁴ D-Dimers,^{20, 25, 26} Interleukin-6,^{21, 24, 27} von Willebrand factor,^{28, 29} S-100 β ,³⁰ and neuron specific enolase (NSE),³¹ have been associated with functional outcome or mortality, only a few biomarkers added to prognosis based on clinical assessment. None of these markers, however, were fully evaluated including assessment of accuracy (i.e. calibration by goodness-of-fit test), discriminatory ability (i.e. C-statistics), reclassification improvement, and performance in an external validation study

according to the recommendations of the American Heart Association for studies evaluating biomarkers in cardiovascular research. ³²

Several prognostic models have been evaluated in the past years. Some of these models include information from MR³³ or CT³⁴, others are based mostly on clinical information such as comorbidities or stroke severity^{35, 36, 37}. As reference for reclassification, we chose the prognostic index of König *et al* because of its validation for both functional outcome and mortality at 3 months along with its robust prognostic power arising from two easily accessible variables such as age and NIHSS.¹⁹ In order to be used in clinical routine, prognosis should be almost immediate and based only on a few variables, thus copeptin, which adds to the simple and highly accurate prognostic index by Koenig *et al*¹⁹ may be promising. Measurement of copeptin in the emergency setting (incubation time 30 minutes⁶) may help physicians to more accurately inform patients and care givers upon the overall prognosis. Copeptin might help in early decision making on aggressiveness of care, potential new interventions, discharge planning and rehabilitation. In the setting of trials of new stroke therapies, it might also be valuable predict those with stroke recovery. For optimal risk stratification, it is crucial that prognostic information is available within the first hours from symptom onset and copeptin meets this demand. The pathophysiological mechanism relating copeptin with stroke outcome and mortality is only partially understood. Copeptin derives from a larger precursor peptide along with vasopressin (AVP) and is released in an equimolar ratio to AVP. The advantage of copeptin is that it is more stable in blood circulation and easier to measure compared to AVP. ¹⁴ The secretion of AVP can be stimulated through brainstem and limbic pathways triggered by different “stressors”, it seems to act as an endogenous barometer of integral homeostasis. Thus copeptin assesses the severity of damage beyond lesion size, the effect of age, gender, and measurable clinical impairment on admission. In addition AVP/copeptin might be associated with ACTH-induced

hypercortisolism, which is thought to potentiate ischemic neuronal injury, especially in the long run.³⁸ Data from experimental studies imply that AVP plays a role in brain edema formation as blocking of AVP receptors attenuates brain edema in ischemic mice models.³⁹

Some limitations merit attention. To assess complications, a time-to-event analysis would have been ideal. However, we were not able to document the exact time of onset of some complications, e.g. aspiration pneumonia, and we did not take into account the duration of hospitalisation. Moreover, this study was only powered for the combined endpoint of complications after stroke, but not to assess each complication separately: our subgroup analyses should be interpreted with caution and further studies are needed to elucidate the specific association with each of the assessed complications.

In patients with ischemic stroke, copeptin is a validated blood marker that adds predictive information on functional outcome and mortality at three months beyond important clinical variables such as stroke severity and age. Copeptin appears as a promising blood marker for prediction of in-hospital complications.

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Figure Legends

Figure 1: Flowchart of patient enrollment and follow up.

Figure 2: Kaplan–Meier survival estimates for patients stratified by copeptin tertiles. The numbers of patients at risk are indicated at multiple of 10 days. Overall, Kaplan–Meier survival curves of patients stratified per copeptin tertiles differed ($P < 0.001$, logrank test)

Tables

Table 1. Baseline Characteristics of All Patients, Stratified by Outcome

	All Patients (n = 783)	Favorable Outcome (n = 483)	Unfavorable Outcome (n = 300)	P Value
Demographic data				
Age, median (IQR), y	71.0 (60.5–80.0)	66.2 (58.0–76.0)	77.3 (68.3–83.2)	<.001
Women, n (%)	298 (38.1)	162 (33.5)	136 (45.3)	0.001
Medical history, n (%)				
Hypertension	539 (68.8)	312 (64.6)	227 (75.7)	0.001
Atrial fibrillation	153 (19.5)	77 (15.9)	76 (25.3)	0.002
Current smoking	138 (17.6)	98 (20.3)	40 (13.3)	0.01
Diabetes mellitus	125 (16.0)	59 (12.2)	66 (22.0)	<.001
Coronary heart disease	149 (19.0)	75 (15.5)	74 (24.7)	0.002
Dyslipidemia	432 (55.2)	280 (57.8)	152 (50.7)	0.001
Previous cerebrovascular event	152 (19.4)	86 (17.8)	66 (22.0)	0.16
Modified Charlson Index	0 (0–1)	0 (0–1)	1 (0–2)	<.001
Kidney impairment*	174 (22.2)	82 (17.0)	92 (30.7)	<.001
Clinical data, median (IQR)				
NIHSS at admission (points)	6 (3–13)	4 (2–7)	13 (7–18)	<.001
Body Mass Index (kg/m ²)	25.8 (23.2–28.4)	25.9 (23.4–28.7)	25.6 (22.6–27.8)	0.14
OCSF				
TACS	158 (20.2)	35 (7.1)	123 (41.0)	<.001
PACS	291 (37.2)	191 (39.5)	100 (33.3)	0.09
LACS	188 (24.0)	161 (33.3)	27 (9.0)	<.001
POCS	146 (18.6)	96 (19.9)	50 (16.7)	0.30
Laboratory values, median (IQR)				
Copeptin (pmol/l)	14.2 (5.9–46.5)	9.6 (4.7–25.8)	32.2 (11.8–103.5)	<.001
Time to blood collection (hours) [†]	2.8 (1.7–5.0)	2.7 (1.7–4.6)	3.0 (1.6–5.7)	0.33
Glucose (mmol/l)	6.3 (5.5–7.5)	6.0 (5.4–7.2)	6.7 (5.8–8.3)	<.001
CRP (mg/l)	3.0 (3.0–6.0)	3.0 (3.0–5.0)	3.0 (3.0–9.0)	<.001
Creatinine (mmol/l)	81.0 (69.0–95.0)	80.0 (69.0–92.0)	82.0 (69.0–100.0)	0.27
eGFR (ml/min/1.73m ²) [‡]	75.0 (60.9–91.9)	77.6 (64.7–92.8)	70.5 (55.4–90.1)	<.001
Lesion size on MR, DWI[§]				
None detected	39 (7.3)	32 (8.6)	7 (4.2)	0.07
Small (1–10mm ³)	233 (43.4)	197 (53.1)	36 (21.7)	<.001
Medium (10–100mm ³)	205 (38.2)	128 (34.5)	77 (46.4)	0.02
Large (>100mm ³)	60 (11.2)	14 (3.8)	46 (27.7)	<.001
TOAST subtype, n (%)				
Large-vessel disease	110 (14.0)	64 (13.2)	46 (15.3)	0.46
Cardioembolic	308 (39.3)	183 (37.9)	125 (41.7)	0.29
Small-artery disease	45 (5.8)	40 (8.3)	5 (1.7)	<.001
Multiple causes	70 (8.9)	52 (10.8)	18 (6.0)	0.03
Other known	29 (3.7)	17 (3.5)	12 (4.0)	0.85
Undetermined	221 (28.2)	127 (26.3)	94 (31.3)	0.14

Footnote: mRS, modified Rankin scale; IQR, interquartile range, meaning range between the first and third quartile; NIHSS, National Institute of Health Stroke Scale; OCSF, Oxfordshire Community Stroke Project classification; TACS, Total Anterior Circulation Stroke; PACS, Partial Anterior Circulation Stroke; LACS, Lacunar Anterior Circulation Stroke; POCS, Posterior Circulation Stroke; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MR, Magnetic Resonance; DWI, Diffusion Weighted Imaging; TOAST, Trial of Org 10172 in Acute Stroke Treatment.¹²

See the “Statistical Analysis” section for a description of this analysis. Because of rounding, percentages may not total 100.

* Kidney impairment was defined as eGFR lower than 60ml/min/1.73m².⁴⁰

† Time to blood collection was calculated in hours from symptom onset (if known).

‡ eGFR was estimated according to the Modification of Diet in Renal Disease (MDRD) Study.⁴⁰

§ Percentages refer to patients where information on DWI lesion was present ($n = 537$). Of the 537 patients undergoing an MR on admission, 371 had a favorable outcome (69.1%) and 166 had an unfavorable outcome (30.9%) within 3 months from stroke. The definition of stroke required an acute focal neurological deficit lasting longer than 24 hours, suggestive of acute stroke, and with no sign of acute intracranial bleeding on cerebral imaging (Computed Tomography or Magnetic Resonance). A visible ischemic lesion on MR imaging was not required for the diagnosis of ischemic stroke.

Table 2. Multivariate Logistic Regression Analysis for Functional Outcome and Cox Regression Model for Mortality

Predictors	Functional Outcome					Mortality				
	OR	95% CI			P	HR	95% CI			P
Age (per year)	1.07	1.04	–	1.09	<0.001	1.04	1.02	–	1.06	<0.001
Hypertension	1.00	0.60	–	1.68	0.99	0.90	0.53	–	1.51	0.68
Diabetes mellitus	1.69	0.88	–	3.26	0.12	1.78	1.03	–	3.11	<0.001
Atrial fibrillation	0.69	0.39	–	1.22	0.20	1.14	0.66	–	1.96	0.64
Modified Charlson Index (per point)	1.06	0.89	–	1.27	0.50	1.11	1.01	–	1.23	0.04
Kidney Impairment [†]	1.17	0.69	–	1.99	0.55	1.36	0.86	–	2.16	0.19
NIHSS at admission (per point)	1.14	1.09	–	1.21	<0.001	1.05	1.02	–	1.08	<0.001
TACS	1.98	0.97	–	4.04	0.06	2.02	1.17	–	3.49	0.01
Log ₁₀ (Copeptin [pmol/l])*	2.17	1.46	–	3.22	<0.001	2.40	1.60	–	3.60	<0.001
Log ₁₀ (Glucose [mmol/l]) *	0.55	0.07	–	4.50	0.58	0.68	0.10	–	4.66	0.69
Log ₁₀ (CRP [mg/l])*	1.77	0.99	–	3.17	0.05	1.89	1.20	–	2.96	0.01
Large DWI lesion (>100 mm ³)	4.16	1.62	–	10.65	0.003	1.25	0.69	–	2.27	0.47
Time from symptom onset to blood collection (per hour)	1.06	1.01	–	1.11	0.01	1.01	0.97	–	1.06	0.64
Woman	1.06	0.66	–	1.71	0.80	NA	NA	–	NA	NA
Medium DWI lesion (10–100 mm ³)	1.31	0.80	–	2.14	0.28	NA	NA	–	NA	NA
Unclear cause of stroke	NA	NA	–	NA	NA	2.23	1.39	–	3.58	0.001

Footnote: Study acronyms are explained in the first footnote to Table 1, if not otherwise specified. OR, odds ratio; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; NA, not applicable, meaning that the variable was not significantly associated with an unfavorable outcome or mortality in the respective univariate analysis. See the “Statistical Analysis” section for a description of this analysis. OR and HR refer to a one-unit increase in the explanatory variable and to any 10-fold increase in copeptin, glucose, and CRP (log-transformed with a base of 10). For example, the odds of an unfavorable outcome are on average 2.17 times or 117% higher in a patient with a copeptin level of 30.0 pmol/l compared to a patient with a copeptin level of 3.0 pmol/l, after adjustment for the covariates included in the presented logistic regression model. + Kidney impairment was defined as eGFR lower than 60ml/min/1.73m².⁴⁰ Coronary heart disease and eGFR/creatinine were not included in the multivariate model because of collinearity with atrial fibrillation and kidney impairment, respectively.

Table 3. Area under the Curve for Selected Predictors of Functional Outcome and Mortality

Functional Outcome				
Predictors	ROC Area	95% CI		<i>p</i> *
Copeptin [pmol/l]	0.71	0.67	– 0.75	-
NIHSS	0.81	0.78	– 0.84	<0.001
NIHSS + Copeptin [pmol/l]	0.83	0.80	– 0.86	
Model 1	0.86	0.84	– 0.89	<0.001
Model 1 + Copeptin [pmol/l]	0.87	0.85	– 0.90	

Mortality				
Predictors	ROC Area	95% CI		<i>p</i> *
Copeptin [pmol/l]	0.75	0.71	– 0.80	-
NIHSS	0.80	0.77	– 0.84	<0.001
NIHSS + Copeptin [pmol/l]	0.83	0.79	– 0.86	
Model 2	0.86	0.82	– 0.90	<0.001
Model 2 + Copeptin [pmol/l]	0.87	0.83	– 0.91	

Footnote: Model 1, multivariate logistic regression model presented in table 2.

Model 2, cox regression model presented in table 2. * To test the statistical significance of the comparisons of nested vs. whole models, the likelihood ratio test was used as recommended.^{[17](#)}

Figures

Figure 1

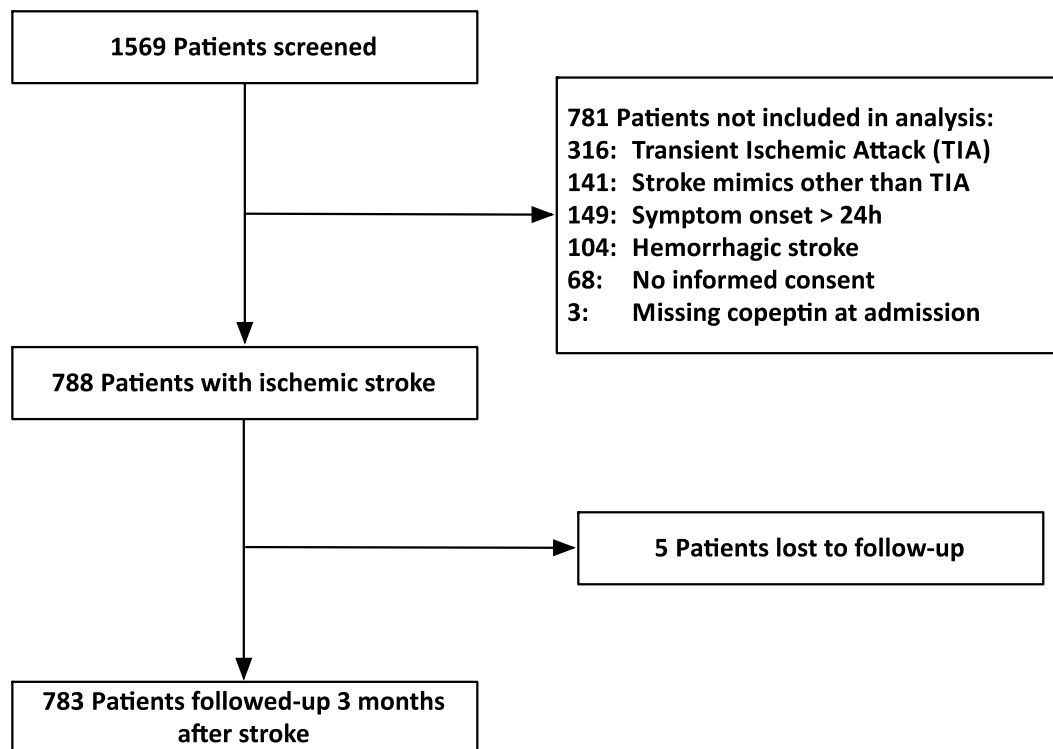


Figure 2

